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# The Potential Value of MRI in External-Beam Radiotherapy for Cervical Cancer

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## Abstract

The reference standard treatment for cervical cancer is concurrent chemoradiotherapy followed by magnetic resonance imaging (MRI)-guided brachytherapy. Improvements in brachytherapy have increased local control rates, but late toxicity remains high with rates of 11% grade ≥3. The primary clinical target volume (CTV) for external-beam radiotherapy includes the cervix and uterus, which can show significant inter-fraction motion. This means that generous margins are required to cover the primary CTV, increasing the radiation dose to organs at risk and, therefore, toxicity. A number of image-guided radiotherapy techniques (IGRT) have been developed, but motion can be random and difficult to predict prior to treatment. In light of the development of integrated MRI linear accelerators, this review discusses the potential value of MRI in external-beam radiotherapy. Current solutions for managing pelvic organ motion are reviewed, including the potential for online adaptive radiotherapy. The impacts of the use of MRI in tumour delineation and in the delivery of stereotactic ablative body radiotherapy (SABR) are highlighted. The potential role and challenges of using multi parametric MRI to guide radiotherapy are also discussed.


*Key words:* Adaptive; cervical cancer; image guided radiotherapy; MR-linac; MRI; organ motion

## Introduction

Locally advanced cervical cancer is treated with concurrent chemoradiotherapy followed by image-guided brachytherapy (IGBT) [1,2]. Over the last 20 years, outcomes have improved due to the addition of chemotherapy and advancement in brachytherapy techniques [3–5]. Long-term side effects are significant, even with the use of IGBT. The retroEMBRACE study, a pan-European multi-centre cohort study reported rates of late toxicity of 11% grade ≥3 [6]. Higher rates of lower-grade toxicity have been reported by patients after treatment [7,8]. The advanced external-beam radiotherapy (EBRT) techniques including intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) are increasingly utilised, with some evidence of side-effect reduction [9–11].

The role of image guidance has evolved since 2000, following the formation of the GEC (Groupe Européen de Curiethérapie)-ESTRO (European Society for Radiotherapy & Oncology) gynaecological working party group [1,12]. Magnetic resonance imaging (MRI) is recommended as the imaging method of choice due to the excellent soft-tissue contrast and visualisation of the tumour [13]. Brachytherapy is an important part of radical radiotherapy treatment for cervical cancer delivering high doses of radiation to the tumour. The value of IGBT has been described in the retroEMBRACE study with 5-year local control rates of 89% and overall survival of 65% [5].

MRI-guided treatment planning is more complex for EBRT than for brachytherapy, requiring electron density information and a whole-body contour for accurate dose

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calculations [13]. To improve integration of MRI into EBRT planning, a number of different technical solutions have been developed. These include a combined MRI and cobalt radiotherapy unit, a MRI scanner on rails, and a linear accelerator combined with an MRI scanner [14].

Potential benefits of these approaches compared to computed tomography (CT) include: (1) MRI simulation allowing for more accurate and reproducible contouring; (2) improved visualisation of the tumour for accurate localised dose escalation with stereotactic ablative body radiotherapy (SABR) in those unsuitable for brachytherapy or those with recurrent disease; (3) imaging during EBRT to allow management of inter- and intra-fraction variations, including online adaptive radiotherapy; and (4) dose-response assessment with multiparametric MRI to guide further treatment.

## Search Strategy

A literature search was carried out in the MEDLINE, EMBASE, and CHINAL databases, using the National Institute for Health and Care Excellence (NICE) healthcare databases advanced search. Both full papers and conference abstracts were identified. This was not a formal systematic review due to the broad nature of the subject matter. Search terms included: 'cervix', 'cervical', 'adaptive', 'radiotherapy', 'radiation', 'motion', 'GTV' 'CTV', 'PTV', 'delineation', 'contouring, 'functional', 'MR', 'MRI', 'DWI', 'BOLD', 'spectroscopy', 'multiparametric', 'response'. Articles were also identified from reference lists. The search was carried out between January and March 2017 with an update in March 2018.

For simplicity in this review, the following clinical target volume (CTV) definitions have been used. The primary CTV includes the upper vagina, cervix, parametrium, and whole uterus (unless specifically stated). The nodal CTV includes the elective nodal areas and as well as any involved nodes, and the combined CTV includes both the primary and nodal CTV.

## Aim

The aim of this review is to explore the value of MRI in treatment planning and online imaging with EBRT for cervical cancer in light of the recent technological developments. The scope includes techniques that allow accurate radiotherapy delivery including management of internal motion as well as the potential of multiparametric MRI.

## Use of MRI for Radiotherapy Simulation and Planning

Although the FIGO (The International Federation of Gynecology and Obstetrics) staging does not mandate cross-sectional imaging, MRI has been shown to be valuable in the accurate assessment of the primary tumour [15]. In comparison to CT, MRI has excellent soft-tissue contrast and is widely used for staging and post-treatment evaluation of cervical cancer, as it has been shown to be superior in assessing tumour size as well as parametrial, bowel, and bladder involvement [16–20]. Nodal assessment, however, has been shown to be sensitive, but not very specific [21]. One of the greatest sources of uncertainty in radiotherapy is that of accurate tumour delineation. Better quality imaging may help to improve this uncertainty [22].

MRI acquisition comprises a trade-off between scan time, image resolution, and signal-to-noise ratio [23]. Some patients are unable to undergo MRI due to implants, such as some pacemakers, and others are unable to tolerate it. Artefacts and distortions can be due to patient motion as well as magnetic field inhomogeneities caused by the equipment or the patient [24]. Many of these can be corrected following image acquisition as long as sufficient quality assurance is in place [24] Consensus MRI simulation protocols have been developed with two-dimensional (2D) T2-weighted turbo spin echo (TSE) sequences recommended [25].

Current consensus recommendations suggest that MRI simulation should be fused with CT simulation images [25]; however, there is potential for MRI-only simulation. Advantages include the need for a single scan with no additional ionising radiation dose and elimination of uncertainties related to co-registration [26]. In some cases there will be a change in position of the pelvic organs on CT and MRI, limiting soft-tissue registration; however, this information may facilitate the development of an internal target volume (ITV), as suggested in the EMBRACE II protocol [27].

Challenges include the need to estimate an electron density map to allow for planning and dose calculations [28,29]. A common approach in the pelvis is to auto-contour different tissues, such as bone, muscle, and fluid, and assign them an electron density, with a commercial solution successfully developed for patients with prostate cancer [29]. Geometrical uncertainties can increase at the edge of the MRI imaging field, and correct sequence selection and quality assurance are needed to ensure an accurate whole-body contour is available for radiotherapy planning [30].

A summary of the benefits and disadvantages of MRI and CT is included in Table 1.

Most interobserver studies using MRI have been performed for brachytherapy target volume delineation. A comparison of CT versus MRI contouring found similar interobserver variation, but with MRI, smaller volumes were contoured [34,35]. The overestimation of the high-risk CTV (HR-CTV) using CT has been confirmed in other studies, and although there has been no histopathological confirmation of MRI volumes in this setting, the excellent clinical outcomes after IGBT suggest that they are sufficiently accurate [36,37]. The correct MRI sequence and orientation is important to ensure accurate contouring [31,38].

There have been no studies comparing MRI with CT-based contours for EBRT. Eminowitcz *et al.* [39] reported up to twofold differences in combined (primary and nodal) CTV volume between multiple observers with CT-based

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